Survey in expert clinicians on validity of automated calculation of optimal cerebral perfusion pressure

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Abstract

BACKGROUND**:** Optimal cerebral perfusion pressure (CPPopt) targeting in traumatic brain injury (TBI) patients constitutes an active and controversial area of research. It has been suggested that an autoregulation guided CPP therapy may improve TBI outcome. Prerequisites of a CPPopt intervention study would be objective criteria for the CPPopt detection.. This study compared the agreement between automated and visual CPPopt detection.

METHODS: Twenty-five clinicians from 18 centres worldwide, familiar with brain monitoring and using dedicated software, reviewed ten 4-hour CPPopt screenshots at 48 hrs after ictus in selected TBI patients. Each screenshot displayed the trends of cerebral perfusion pressure (CPP), intracranial pressure (ICP), cerebrovascular pressure reactivity (PRx) as well as the 'CPP-optimal' curve and its associated value (automated CPPopt). The main objective was to evaluate the agreement between expert clinicians as well as the agreement between the clinicians and automated CPPopt.

RESULTS: Twenty-two clinicians responded to our call (88%). Three screenshots were judged as 'CPPopt not determinable' by > 45% of the clinicians. For the whole group, the consensus between automated CPPopt and clinicians' visual CPPopt was high. Three clinicians were identified as outliers. All clinicians recommended to modify CPP when patients differed > ± 5 mmHg from their CPPopt. The inter-observer consensus was highest in cases with current CPP below the optimal value.

CONCLUSIONS: The overall agreement between automated CPPopt and visual CPPopt identified by autoregulation experts was high, except for those cases when the curve was deemed by the clinicians not reliable enough to yield a trustworthy CPPopt.

BACKGROUND

Optimal cerebral perfusion pressure (CPPopt) targeting in patients with traumatic brain injury (TBI) constitutes an active and controversial area of research that still awaits level I evidence.(1) The notion of CPP-targeted therapy should be framed in the context of cerebral autoregulation—the uninjured brain's response to variations in cerebral perfusion pressure (CPP) through the physiologic relationships between CPP, cerebral blood flow (CBF), and vascular resistance. In healthy individuals CBF is adjusted by means of vasodilatation and vasoconstriction of cerebral vessels, a process responsible for pressure cerebral autoregulation.(2) After severe TBI, cerebral autoregulation is frequently disturbed with CBF becoming to some extent dependent on cerebral CPP.(3) International TBI guidelines recommend keeping CPP between 60 and 70 mmHg during the whole intensive care unit (ICU) admission.(4) It is increasingly felt that CPP management in TBI should be carefully individualized to the patient to maximize benefit and minimize harmful side effects of unnecessary or inappropriate interventions.(5)' (6) However, exactly on what basis this should be done is a matter of debate. It is plausible that targeting a CPP where autoregulation is best preserved may be one possible strategy that clinicians might use when balancing the dangers of hypo or hyperperfusion in a disease that is fundamentally heterogeneous.(7)

Cerebrovascular pressure reactivity is a simple method of assessing globally averaged cerebral autoregulation. For patients with closed head injury, it can be easily inferred from the pressure reactivity index, PRx (figure 1).(8)

Negative PRx values reflect a reduction in ICP in response to an increase in MAP indicating intact vascular pressure reactivity, whereas positive values, conversely, indicate impairment. Due to the fact that it can be determined from periodic variations in ICP and MAP without needing external stimuli, the PRx has become widely accepted as a marker for cerebral autoregulatory status in many neurocritical care settings.(5) Plotting PRx against CPP will often generate a "U" shaped curve, the minimum of which represents the CPP (CPPopt) corresponding to the smallest value of PRx where the cerebral autoregulation response is most active (figure 1). CPPs both above and below CPPopt are associated with worsened cerebrovascular reactivity and with worse outcome.(7;9)

The 2014 neuromonitoring guidelines promote the concept of autoregulation based monitoring and treatments.(5) To this end curve fitting software and heuristics have been

developed so that the CPPopt can be automatically calculated and displayed bedside (figure 2).(10) Whilst observational data is encouraging, a prospective randomised evaluation of CPPopt-targeted therapy is urgently required to determine whether CPPopt is purely prognostic, or if CPPopt represents a true physiologic target that, if achieved, will improve patient outcomes.

However it is well known that CPPopt curves may be noisy and, in some cases, absent or only partially present meaning that a degree of physician assessment and interpretation of the autoregulation data is necessary. Before a prospective CPPopt guided intervention study could be set up , it is a crucial first step to assess the reliability and (face) validity of automated CPPopt calculation and display. If this is not the case, then large inter-rater variability means that CPPopt guided therapy is physician dependent and therefore a prospective intervention study will fail on its clinical feasibility.

In this survey the primary objective was to test the agreement between the automatically generated CPPopt values (automated CPPopt) and the values deduced from inspection the CPPopt curve by clinicians with expertise interpreting CPPopt and PRx (clinicians' visual CPPopt). If clinicians with experience cannot agree then CPPopt guided therapy cannot realistically be deployed at the bedside. We aimed to identify factors that might be associated with disagreement. Furthermore, a CPPopt based treatment algorithm currently does not exist and as a secondary objective it is important to explore how clinicians would adapt therapy if a patient's current CPP deviates from CPPopt.

METHODS

Participants In this cross-sectional survey, 25 intensivists, neurologists and neurosurgeons in 18 different centres were contacted by email in April 2014. They were all familiar with the CPPopt and PRx concept and/or have been publishing in the field of autoregulation research. No special training or documentation was offered related to the interpretation or future use of the CPPopt methodology.

Survey All participants were sent a questionnaire that consisted of an introduction, 20 screenshots of 10 selected TBI patients with for every patient two screenshots, a 48 hour monitoring overview and a 4 hour monitoring screenshot 48 hours after trauma ictus. The latter was the screenshot of interest (figure 2) and the participants were asked to study this screenshot in depth and answer two sets of questions (table 1).

Overview screenshot In the introduction of the questionnaire we provided an explanation of the structure of the survey and the displayed physiological variables.. We started with an 48 hour overview of the ICP/CPP monitoring trends and a CPPopt curve covering the 48 hour (CPPopt 48 hours) period. In this overview the exact timing of the 4 hour monitoring screenshot was displayed. The reason for this was that in case a CPPopt curve was not present at the 48 hour time point, we moved one hour forward till the first 4 hour CPPopt curve would appear.

4 hour screenshot The following physiological variables were displayed in the 4 hour CPPopt screenshot: 1-minute values of ICP/MAP/CPP, trends of median CPP and CPPopt, PRx colour bar (with dichotomization of PRx into intact (green, PRx <0.3) or impaired (red, PRx>0.3) cerebrovascular pressure reactivity simplifying autoregulation status over time),(11) the CPPopt curve (PRx error bar versus 5 mmHg CPP intervals plot with the CPPopt fitted curve and automated CPPopt value), and a histogram showing the distribution of time spent in the different 5 mmHg CPP intervals (figure 2). The PRx error bar represents the median ± precision of PRx values in a 5 mmHg CPP interval using 4 hours of monitoring data. PRx is calculated as a moving correlation coefficient composed of repeated statistical Pearson correlations between mean arterial (blood) pressure (MAP) and intracranial pressure (ICP). The method incorporates the philosophy of assessing active cerebrovascular reactions by observing the response of cerebral blood volume and subsequent ICP to slow spontaneous changes in MAP.(12) Whilst PRx is not a perfect measure of autoregulatory capacity and does not reflect focal variations, it has the great advantage of being available in near real-time.

Patients The screenshots were taken from 10 selected TBI patients admitted at the University Medical Center Groningen (the Netherlands) during the period 2012 to 2014. In this period 35 TBI patients with ICP monitoring were admitted and monitored. All patients had ICP monitoring and treatment according to international TBI monitoring guidelines.(13;14) ICP/CPP had to be recorded for at least three days for selection for this study. No demographic, clinical or diagnostic information were provided. The local medical ethical committee waived consent for the anonymized data collection and retrospective data analysis in TBI patients with ICP monitoring (University Medical Center Groningen, The Netherlands).

Questions For each 4 hour screenshot the clinicians were asked1) either to identify the CPPopt visually (clinicians' visual CPPopt) or to indicate whether CPPopt is undeterminable, 2) to decide which CPP out of four options they would target within the next hours when faced with the current patients' CPP (table 1).

Statistical analysis

Level of CPPopt agreement The difference between the clinicians' visual CPPopt (question one) and the automated CPPopt was calculated and averaged per screenshot and per clinician and presented as the mean ± standard deviation (SD) with 95%-confidence intervals (95%-CI). We hypothesized that the group average would be close to zero with small 95%-CI intervals. Only cases with a clinicians' visual CPPopt were used in these calculations. In addition, the calculated differences were categorized (%) in four groups: 1) CPPopt not determinable. 2) no difference (0 mmHg). 3) difference within the range of ± 5 mmHg. 4) difference $\leq$ -5 or $\geq$ 5 mmHg (table 1). An outlier in the last group was identified after redefining individual responses by a *Z*-score > 3.29 in Statistical Package of Social Sciences (SPSS).

Near future CPP targets From the clinicians who identified CPPopt, the deviation between the clinicians' visual CPPopt value and the current patients' CPP (question two) was calculated and called 'CPP_difference'. The four treatment options (from question two) were reclassified into: 1) 'Do nothing'. 2)'Increase CPP'. 3) 'Decrease CPP' (table 1). The treatment option 'Reach for the automated CPPopt' was changed to 'Increase CPP' when the CPP_difference was negative (theoretically 'hypoperfusion') and to 'Decrease CPP' when the CPP_difference was positive (theoretically 'hyperperfusion'). A one-way analysis of variance (ANOVA) test was used to compare the mean CPP_difference values for the three CPP therapy options. In addition, the CPP_difference variable was divided into seven 5 mmHg categories, whereby the distribution of CPP therapy options was analysed. A *p*-value <0.05 was considered as statistically significant. Statistical analysis were computed in SPSS, version 21.

RESULTS

Twenty-two clinicians returned the questionnaire (response rate 88%, online supplementary material table S1). 96% of the two questions were completely answered and could be used

for analysis. Missing data were mainly due to the fact that by mistake clinicians used the 48 hour monitoring overview (CPPopt 48 hours) instead of 4 hour screenshot(CPPopt).

Question 1 *Agreement with automated CPPopt* From the 219 returned answers (only one missing), 157 (72%) were answered with a CPPopt value and 62 (28%) were answered with CPPopt 'not determinable'. Figure 3 shows the distribution between automated CPPopt and clinicians' visual CPPopt. From these 157 clinicians' answers, seventy-two (46%) completely agreed with the automated CPPopt value. In seventy-six answers (48%) they agreed within a range of ± 5 mmHg. In only nine answers (6%) the clinicians' visual CPPopt differed > ± 5 mmHg from the automated CPPopt. Figure 4 shows the difference between the automated and clinicians' CPPopt per screenshot (figure 4a) and per clinician (figure 4b). For the whole group the mean calculated difference between automated and clinicians' visual CPPopt was 0.01 mmHg (95%-CI: -031 to 0.33, n=157) (online supplementary material, table S2 and S3). The mean value of absolute difference between automated and clinicians' visual CPPopt was 0.99 mmHg (95%-CI: 0.72-1.28, n=157).

Outliers Four answers (of three clinicians) were classified as outliers. They were contacted by email. One clinician replied to have chosen the CPP value on the descending part of the autoregulation curve whereby PRx was getting negative and not going for the CPP with the most negative PRx covered by the curve. Another replied that the present CPPopt curve was not convincing and therefore a (higher) CPP was chosen with a lower PRx value (referring to the 'best' autoregulation condition).

CPPopt not determinable In three screenshots > 45% of the clinicians indicated that CPPopt was 'not determinable' (screenshot 5, 8 and 10; figure 5). By comparing these screenshots with the other seven, these less reliable automated CPPopt curves had asymmetrical U-shaped curves, not covering both positive and negative PRx values, only covering a limited range of CPP intervals, or more than one curve could be fitted visually (figure 2B). Screenshots with a CPPopt that were judged 100% determinable were well-covered by the available 5 mmHg CPP intervals, covering both positive and negative PRx values and were symmetrical U-shaped (figure 2A).

Question 2 *Therapy choices based on differences between current CPP and clinicians' visual CPPopt* For the three CPP therapy options the mean CPP_difference was significantly different: 0.6 mmHg (SD 3.6) for option 'Do nothing', 6.9 mmHg (SD 4.2) for option 'Decrease CPP', and -11.0 mmHg (SD 3.8) for option 'Increase CPP' (ANOVA F: 206, $p < 0.001$). To find

out at which value clinicians decide to change their CPP therapy, the CPP_difference was divided in seven categories and compared per CPP therapy option (online supplementary material, table S4). The main decision (> 90%) is to 'Do nothing' with the difference being between 5 to -5 mmHg. CPP would be increased by 83% of clinicians with CPP_difference being between -5 and -10 mmHg. With an even bigger difference, more than 90% of clinicians decided to increase CPP. With a CPP_difference between +5 to +10 mmHg, there is less consensus about the CPP policy: 60% indicates not to change CPP and 40% decided to decrease CPP.

DISCUSSION

The CPPopt concept is a promising 'biological plausible' target that uses cerebrovascular pressure reactivity to guide individual CPP therapy in severe TBI patients. CPPopt needs to be evaluated urgently in prospective intervention studies before recommendations can be made as to how, or indeed if, it should be integrated into clinical decision making.(15)
In this survey we showed a high level of agreement between the choices of a selected international group of clinicians and the automated CPPopt value. The approached clinicians were selected from a sub-pool of individuals who are familiar with PRx and/or CPPopt monitoring. It therefore would seem an essential first step to ensure that the technique is reproducible amongst "experts" before even contemplating rolling it out further. Any subsequent intervention study would similarly be attempted in a small group of 'expert' ICUs.

Overall rating of face validity of automated CPPopt (question 1) The overall agreement between the automated CPPopt and visual judgement was excellent when the PRx-CPP relationship followed a reasonably well defined U shape curve. However, in 3 screenshots a large percentage of clinicians found the fitted CPPopt curve not reliable enough to retrieve a convincing CPPopt. In addition, four answers (from 3 clinicians) could be labelled as outliers. In-depth examination of these results revealed important clues for clinicians doubting the automated CPPopt value. As it appeared, the visual CPPopt detection of a curve is found less reliable if the underlying PRx-CPP relationship is asymmetrical , does not cover both positive and negative PRx values, only covers a limited CPP range, and if more than one curve can be fitted visually (figure 2B). Currently we are working on improving the automated CPPopt algorithm by incorporation of multiple-(time) window calculations with the hypothesis that it improves the continuity and stability of CPPopt significantly.(16;17) In addition we are

evaluating the influence of CPPopt calculation weighting factors like time, PRx-CPP curve shape, curve fit errors and autoregulation status on automated (multi-window) algorithm performance.

CPP guided therapy (question 2) Most clinicians decided to change CPP in the direction of their selected CPPopt when the absolute difference between the patients' current CPP and clinicians' visual CPPopt was > 5 mmHg whereby CPP below optimal reaches very high consensus for therapy change. CPP above optimal leads to a more variable decision. For the set-up of a CPPopt feasibility study, the current ICP/CPP oriented treatment algorithm should be adapted with individual CPPopt targets replacing the current 60-70 mmHg CPP guideline range. Also in other brain pathologies an individual and up-to-date cerebral perfusion target is probably of benefit during intensive care admission. The results of this study might help with the set-up of other 'optimal' targeted therapy intervention study initiatives in acute stroke, neonatology and post-cardiac arrest patients.(18-20)

Limitations The 22 clinicians are all active in autoregulation research and are all familiar with the CPPopt method. The selection was chosen as a pragmatic one but therefore not an exclusive list of world-wide expertise. Furthermore we cannot be sure from our result that this will generalize to 'non-expert' practice. But expert consensus/ reproducibility is a pre-requisite for such generalizability. With the screenshots, only limited physiological information, no clinical results and limited answer options were provided. More specific and complete (lengthy) screenshots or clinical scenarios with open answers might have yielded different responses but probably decreased the survey response rate, increased the heterogeneity of the answers and distracted from the main objective of this study.

Questionnaire validity It is difficult to validate a (relatively) small scale questionnaire and we did not attempt to do so formally. Face-validity of our survey was, however, assured by consensus between the authors. It is also important to stress the fact that no golden standard is present for cerebral autoregulation or CPPopt related results.

Future studies With the results of this survey we think we have made an essential step towards further design of the first CPPopt feasibility study, which will be an entry point towards a proper randomized 'CPPopt targeted' versus 'current standard treatment' TBI intervention trial. Even with a positive outcome we would not support a final strategy of just treating an individual number, like CPPopt, rather than the whole patient, particularly in the context of severe TBI. Such approaches to intensive care have failed historically. (14;21;22)

At the moment we can only conclude that for planned intervention studies both the automated value and the PRx-CPP plot (figure 2) should be available for testing of CPPopt guided management at the bedside to yield a trustworthy CPPopt.

CONCLUSIONS The overall agreement between the automated CPPopt value and the value identified by autoregulation experts clinicians was high, except for those cases when the fitted curve was deemed by clinicians not reliable enough to yield a trustworthy CPPopt. Possible solutions like automated weighting and (multiple) averaging are currently under investigation. When CPPopt deviated more than 5 mmHg from the current patients' CPP, the majority of clinicians opted to change therapy. Any benefit of CPPopt guided therapy or other more sophisticated CPP based treatments needs to be proven in prospective studies.

Key messages

- Autoregulation guided cerebral perfusion pressure (CPPopt) therapy in TBI patients constitutes an active and controversial area of research

- Prerequisites of a CPPopt intervention study would be objective criteria for the CPPopt detection (automated CPPopt display) at the bedside

- The overall agreement between the automated CPPopt value and the visual CPPopt value identified by autoregulation experts was high, except for those cases when the fitted curve was deemed not reliable enough to yield a trustworthy CPPopt

- Any benefit of CPPopt guided therapy or other more sophisticated CPP based treatments needs to be proven in prospective studies with incorporation of automated weighting and averaging methods

Figures headings

Figure 1 Schematic depicting the theoretical relationship between CPP and PRx including estimation of CPPopt

Figure 2A Example of 4 hour monitoring screenshot used in the survey

Figure 2B Example of 4 hour monitoring screenshot used in the survey

Figure 3 Distribution of automated CPPopt and clinicians' visual CPPopt (scatterplot)

Figure 4A Mean difference between automated CPPopt and clinicians' visual CPPopt calculated per 4 hour screenshot

Figure 4B Mean difference between automated CPPopt and clinicians' visual CPPopt calculated per clinician

Figure 5 Number of clinicians appointing a CPPopt value or 'CPPopt not determinable' for each 4 hour screenshot

Figure legends

Figure 1 The relationship between CPP and PRx can be approximated by fitting an U-shaped curve (2nd order polynomial mathematical function) automatically whereby with both high or low values of CPP, the cerebral pressure reactivity (PRx) is impaired (top right panel, red). However, for intermediate CPP values, PRx is (probably) working (bottom right panel, green) and the CPP at which PRx is most negative is termed the 'optimal' CPP (CPPopt, black dot).

Abbreviations: CPP(opt) indicates (optimal) cerebral perfusion pressure, PRx, pressure reactivity index.

Figure 2 A + B Patient cerebral monitoring screenshot representing 4 hours of monitoring. In the upper graph the MAP (blue), CPP (yellow) and ICP (white) are shown. The second graph shows trends of CPP (yellow) and CPPopt (red). The coloured bar is green when PRx is < 0.3 and red when PRx is > 0.3, representing working and impaired pressure reactivity respectively.(11) Underneath the green bar, the features of the CPPopt curve are shown (yellow). This curve is automatically fitted through the mean of the binned PRx error bars.(7) CPPopt is the CPP where PRx is at its lowest value, which has a value of 70 and 94 mmHg in screenshot A and B, respectively. The bottom graph shows the percent of time that the CPP was in each 5 mmHg CPP interval during the 4 hour period.
Abbreviations: MAP indicates mean arterial (blood) pressure, CPP(opt), (optimal) cerebral perfusion pressure, ICP, intracranial pressure, PRx, pressure reactivity index.

Figure 3 Scatterplot of the automated CPPopt versus the clinicians' visual CPPopt (n=157).
Abbreviations: CPP(opt) indicates (optimal) cerebral perfusion.

Figure 4 A Mean difference between automated CPPopt and clinicians' visual CPPopt calculated per screenshot. **B** Mean difference between automated CPPopt and clinicians' visual CPPopt calculated per clinician. Larger (grey) bullets represent mean values. Smaller bullets represent individual CPP differences between automated and visual numbers.
Abbreviations: CPP(opt) indicates (optimal) cerebral perfusion pressure.

Figure 5 The x-axis shows the 10 patient 4 hour screenshots and the y-axis shows the number of clinicians who appointed a CPPopt value (black) or 'CPPopt not determinable' (grey). Numbers represent the responses of the clinicians.
Abbreviations: CPP(opt) indicates (optimal) cerebral perfusion pressure.

Online supplementary materials

Online supplementary material table S1 List of responding participants for the survey.

Online supplementary material table S2 Difference between the individual clinicians' visual CPPopt and automated CPPopt value per screenshot.

Online supplementary material table S3 Difference between the individual clinicians' visual CPPopt and automated CPPopt value per clinician.

Online supplementary material table S4 The different therapy options for the categorized deviation from patients' CPP from CPPopt.

Reference List

(1) Prabhakar H, Sandhu K, Bhagat H, Durga P, Chawla R. Current concepts of optimal cerebral perfusion pressure in traumatic brain injury. J Anaesthesiol Clin Pharmacol 2014;30:318-27.

(2) Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989;20:45-52.

(3) Bouma GJ, Muizelaar JP. Cerebral blood flow, cerebral blood volume, and cerebrovascular reactivity after severe head injury. J Neurotrauma 1992;9 Suppl 1:S333-S348.

(4) Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery 2017;80:6-15.

(5) Le Roux P, Menon DK, Citerio G, Vespa P, Bader MK, Brophy GM et al. Consensus summary statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care : A statement for healthcare professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Intensive Care Med 2014;40:1189-209.

(6) Robertson CS, Ropper AH. Getting Warmer on Critical Care for Head Injury. N Engl J Med 2015;373:2469-70.

(7) Aries MJ, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med 2012;40:2456-63.

(8) Czosnyka M, Smielewski P, Kirkpatrick P, Laing RJ, Menon D, Pickard JD. Continuous assessment of the cerebral vasomotor reactivity in head injury. Neurosurgery 1997 ;41:11-7.

(9) Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. Crit Care Med 2002;30:733-8.

(10) Schmidt JM, Kummer BR. Clinical Decision Support for Cerebral Perfusion Optimization After Traumatic Brain Injury. Crit Care Med 2016;44:1958-60.

(11) Sorrentino E, Diedler J, Kasprowicz M, Budohoski KP, Haubrich C, Smielewski P et al. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocrit Care 2012;16:258-66.

(12) Bouma GJ, Muizelaar JP, Bandoh K, Marmarou A. Blood pressure and intracranial pressure-volume dynamics in severe head injury: relationship with cerebral blood flow. J Neurosurg 1992;77:15-9.

(13) Patel HC, Menon DK, Tebbs S, Hawker R, Hutchinson PJ, Kirkpatrick PJ. Specialist neurocritical care and outcome from head injury. Intensive Care Med 2002;28:547-53.

(14) Stocchetti N, Maas AI. Traumatic intracranial hypertension. N Engl J Med 2014 29;370:2121-30.

(15) Lazaridis C, Smielewski P, Steiner LA, Brady KM, Hutchinson P, Pickard JD et al. Optimal cerebral perfusion pressure: are we ready for it? Neurol Res 2013;35:138-48.

(16) Depreitere B, Guiza F, Van den Berghe G, Schuhmann MU, Maier G, Piper I et al. Pressure autoregulation monitoring and cerebral perfusion pressure target recommendation in patients with severe traumatic brain injury based on minute-by-minute monitoring data. J Neurosurg 2014;120:1451-7.

(17) Weersink CS, Aries MJ, Dias C, Liu MX, Kolias AG, Donnelly J et al. Clinical and Physiological Events That Contribute to the Success Rate of Finding "Optimal" Cerebral Perfusion Pressure in Severe Brain Trauma Patients. Crit Care Med 2015;43:1952-63.

(18) Diedler J, Santos E, Poli S, Sykora M. Optimal cerebral perfusion pressure in patients with intracerebral hemorrhage: an observational case series. Crit Care 2014;18(2):R51.

(19) da Costa CS, Czosnyka M, Smielewski P, Mitra S, Stevenson GN, Austin T. Monitoring of Cerebrovascular Reactivity for Determination of Optimal Blood Pressure in Preterm Infants. J Pediatr 2015;167:86-91.

(20) Sekhon MS, Smielewski P, Bhate TD, Brasher PM, Foster D, Menon DK et al. Using the relationship between brain tissue regional saturation of oxygen and mean arterial pressure to determine the optimal mean arterial pressure in patients following cardiac arrest: A pilot proof-of-concept study. Resuscitation 2016;106:120-5.

(21) Stocchetti N, Roux PL, Vespa P, Oddo M, Citerio G, Andrews PJ et al. Clinical review: Neuromonitoring - an update. Crit Care 2013;17:201.

(22) Dias C, Silva MJ, Pereira E, Monteiro E, Maia I, Barbosa S et al. Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study. Neurocrit Care 2015;23:92-102.